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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,746	02/18/2004	Sheldon B. Greer	2954-128	2050

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 22-42 are currently pending and are the subject of this Office Action. Applicants cancelled claims 1-21 in the response filed July 10, 2006.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-13 in the reply filed on July 10, 2006 is acknowledged. Applicant cancelled claims 1-13 and submitted new claims 22-42 in the same reply. Examiner has determined that the newly added claims read on the elected invention and are therefore subject to examination on the merits.

Applicant's election without traverse of the specific combination of 5-chloro-5'-deoxycytidine and tetrahydrouridine in the reply filed on July 10, 2006 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed 2/18/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Reference "U", Greer *et al.*, is not filed on Form PTO-1449. It appears applicant simply attached the PTO-892 form from a prior-filed application. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance

with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-42 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 32 recite the limitation "treating a tumor" in line 1 of each respective claim. This limitation is unclear because it requires that only one tumor be treated. It is not clear how one would selectively treat a single tumor in a subject. Amending the claims to recite "at least one tumor" would overcome this rejection provided there is support in the specification for such an amendment. Claims dependent from claims 22 and 32 are included in this rejection.

Claims 22 and 32 recite the administration of "an effective amount" of 5-chloro-2'deoxycytidine and "an effective amount" of a cytidine deaminase inhibitor. This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the "effective amount" being administered is effective to treat the condition recited in the preamble (*i.e.* "a tumor"). The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be

implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954). Claims dependent from claims 22 and 32 are included in this rejection.

Claims 22 and 32 recite the administration of 5-chloro-2'deoxycytidine and a cytidine deaminase inhibitor "to a subject". This limitation is indefinite because it is not clear that the subject being administered these agents is in need of such administration. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the agents are being administered to a subject in need of treatment (*i.e.* a subject with a tumor). Claims dependent from claims 22 and 32 are included in this rejection.

Claims 22 and 32 recite exposing "the subject" to "an effective level of radiation". The claims are indefinite because it is not clear what the radiation is effective for. Thus, the limitation "effective level" is not clear. Claims dependent from claims 22 and 32 are included in this rejection.

Claims 30 and 40 recite the limitation "said radiation source" in line 1. There is insufficient antecedent basis for this limitation in the claims.

Claim 31 and 41 recite the limitation "said radionuclide" in line 1. There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22-23, 25-27, 29, 32-33, 35-37, 39 and 42 are rejected under 35 U.S.C. § 103(a) as being obvious over Russell *et al.* (Applicant IDS Reference "AJ") in view of Nagatake *et al.* (Cancer Research, 1996, vol. 56, pages 1886-1891).

The instant claims are drawn to methods of treating "a tumor" caused by hypermethylation of nucleic acids by administering 5-chloro-2'deoxycytidine and tetrahydrouridine with subsequent exposure of the tumor to radiation.

Russell *et al.* disclose that cancer cells are sensitized to radiation by 5-chloro-2'deoxycytidine (Cld/Cyd) (Abstract). Tetrahydrouridine (H_4Urd) is co-administered with Cld/Cyd in the methods taught therein (Figure 1; Figure 2; "Results"). Figure 2 (page 2884) demonstrates that RIF-1 cells treated *in vivo* with continuous infusion of Cld/Cyd and H_4Urd and subsequently excised and exposed to X-rays resulted in greater cell death than those tumor cells treated with saline. Russell *et al.* also disclose that Cld/Cyd is a promising compound for sensitizing tumors because it is a better substrate for deoxycytidine kinase than previously brominated and iodinated cytidines (page 2885, right column, second paragraph). Further, it is disclosed that "[E]ffective methods of blocking the catabolism of these drugs have been reported, using uracil derivatives to block cytidine deaminase" (page 2885, right column, third paragraph). Russell et al. do not disclose the treatment of tumors cause by hypermethylation of nucleic acids.

However, Nagatake *et al.* disclose that altered DNA methylation may play a role in the oncogenesis of human neoplasms, including lung cancer (Abstract). It is well known in the art that alterations in the pattern of DNA methylation are a consistent molecular change in human cancers (page 1886, left column, first paragraph). Further, these abnormalities include "regional hypermethylation" and an "overall increase in DNA methyltransferase activity that catalyzes

DNA methylation". Evidence of inactivation of well-defined tumor suppressor genes by aberrant hypermethylation has been reported in a limited number of human cancers (page 1886, left column, first paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the methods disclosed in Russell *et al.* to treat tumors caused by the hypermethylation of nucleic acids. It is well known in the art that hypermethylation of tumor suppressor genes is a cause of cancerous tumors as evidenced in Nagatake *et al.* In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed methods would have been *prima facie* obvious in view of the Russell and Nagatake disclosures.

Claims 22- 42 are rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871; Published May 9, 1985) in view of Nagatake *et al.* (Cancer Research, 1996, vol. 56, pages 1886-1891) and Shepherd *et al.* (Cancer, 1992, vol. 70, pages 2250-2254, Abstract).

Greer discloses a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). The invention disclosed provides therapeutic materials and procedures for treating solid tumors using X- or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-15). According to one aspect of the invention of WO '871, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until

amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds.

Greer does not disclose the treatment of tumors caused by hypermethylation of nucleic acids or the use of yttrium-90 as a radiation source.

However, Nagatake *et al.* disclose that hypermethylation of DNA is recognized as a consistent molecular change in human cancers, including lung cancer (page 1886, left column, first paragraph).

Shepherd *et al.* disclose that yttrium-90 microspheres have been used in the treatment of primary hepatocellular carcinoma (Abstract).

Thus, the instantly claimed methods of treating tumors caused by hypermethylation of nucleic acids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Greer discloses a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). Nakatake *et al.* disclose that altered DNA methylation may play a role in the oncogenesis of human neoplasms, including lung cancer. Shepherd *et al.* disclose yttrium-90 is a radiation source used in the treatment of cancer. The skilled artisan would be imbued with at least a reasonable expectation that the methods disclosed in Greer could

be used to treat tumors caused by hypermethylation of nucleic acids and that yttrium-90 would be a viable source of radiation in such a treatment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,933,287. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

courts have determined that "consisting essentially of" can be construed as an equivalent of "comprising".

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).

It is the examiner's position that the inclusion of 4-N-methyl FdC as required in the methods of the '287 patent would not materially affect the basic and novel characteristics of the instantly claimed methods. Further, the court has held that:

> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, *e.g.*, *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Examiner finds no such "clear indication" in the specification or the claims of what the basic and novel characteristics actually are. Thus, the interpretation of the instant claims to be drawn to methods "comprising" the recited steps is appropriate.

> If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964).

Thus, the language of the instant claims allows for the inclusion of 4-N-methyl FdC in the claimed methods thereby rendering the instant methods unpatentable over claims 1-9 of the '287 patent.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

August 8, 2006

Ardin H. Marschel 8/17/06
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SUPERVISORY PATENT EXAMINER